Molecular models should not be published without the corresponding atomic coordinates

Stephen C. Graham[1], Bhushan Nagar[2], Gil G. Privé[3] and Janet E. Deane[4]

[1] Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB21QP, UK

[2] Department of Biochemistry, McGill University, Montreal, H3G0B1, Canada

[3] Princess Margaret Cancer Centre, Toronto, M5G 1L7, Canada

[4] Cambridge Institute for Medical Research, Cambridge Biomedical Campus, Hills Rd, Cambridge, CB20XY, UK

In PNAS, Romero et al (1) present models of how glucocerebrosidase (GCase) interacts with saposin C (SapC) and membranes. Unfortunately, the authors did not publish representative atomic co-ordinates or molecular dynamics trajectories for their models, denying researchers the opportunity to scrutinise the data they used to draw their functional conclusions. Access to this data is an important issue for structural biologists (2) and the open release of experimentally-determined structural data has been the accepted practice for many years (3). Indeed, the Romero paper relied upon several such publically-available structures to carry out their study.

Two specific issues with the Romero paper highlight how the availability of coordinate data would help the community better understand the insights claimed in this manuscript. The first concerns the orientations of SapC and GCase relative to each other and to the membrane. The soluble GCase enzyme cleaves the polar glucose head group from the hydrophobic lipid tails of glucosylceramide, requiring the hydrophobic lipid tails to be shielded from aqueous solvent and/or for GCase to become tightly membrane-associated. SapC has been shown to disrupt lipid bilayers and is thought to facilitate GCase access to substrate at the membrane surface (4). While the molecular dynamics studies in (1) were all performed in the presence of lipid bilayers, Figure S2 is the only illustration of GCase-SapC membrane association. This figure does not clearly show how SapC is oriented relative to GCase and the membrane, nor does it clearly illustrate the molecular interactions between GCase and lipids. In the absence of such details it is impossible to draw any conclusions regarding this very important process of membrane association. The second issue relates to the conformation of SapC when in complex with GCase. The hydrophobic surface that binds lipid tails is inaccessible in the closed form of SapC (5), yet this was the form of SapC used for the molecular dynamics simulations in the presence of GCase and lipids (CPX, Table 1). The authors do not describe how SapC interacts with lipids in their simulations and provide only limited views of the GCase-SapC interfaces in their various complexes. Worryingly, these show the apparent unfolding of helices known to be highly stable (Figure S17A) and disruption of a stable disulphide bond (Figure S35) (6). Several conclusions in the paper depend upon these unlikely conformational changes.

A clearer picture of how saposins transfer hydrophobic lipids to soluble hydrolases is essential to the molecular understanding of sphingolipidoses, a family of devastating human diseases. Recent atomic-resolution crystal structures illustrate how saposins or saposin-like domains interact with lysosomal sphingolipid processing enzymes: the complex between β-galactocerebrosidase and saposin A (7), and the structures of acid sphingomyelinase (8-10). The atomic co-ordinates for these are publicly available. Romero and colleagues missed an opportunity to compare their theoretical model of the SapC-GCase complex with these related, experimentally-determined and validated structures. By not publishing the coordinates illustrated in their figures, they have also prevented the community from independently making such comparisons.

References

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